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10/590,493	06/08/2007	Takahide Kohro	032218A	1082

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,493	KOHRO ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *13-25* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *13-25* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/29/2010 has been entered.

Response to Arguments

2. Applicant's arguments, filed 6/29/2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 13-16 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

5. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, claims 13-16 and 25 recite a method of screening for a substance which improves a vascular cell disorder which

occurs due to the function of Rac protein (i.e., due to the transfer of Rac protein into the nucleus of the cell). Claims 21-24 recite methods of identifying a substance which inhibits the function of Rac protein comprising the same steps as recited by claims 13-16.

6. The MPEP §2163 states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. In the case of chemical entities, Applicant's attention is further directed to *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), which notes that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." While the court recognizes that, "[i]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass" (*Id.*), it is ***also*** recognized that for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim and/or the genus must be sufficiently detailed to show that applicant was in possession of the claimed invention ***as a whole*** (see *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991)). Otherwise, as stated by the court in *Ariad Pharmaceuticals, Inc., v. Eli Lilly and Company* (Fed. Cir. 2010), "a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. **The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus**. In such a case, the functional claim may simply claim a desired result, and may do so without

describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus" (emphasis added).

7. Thus, as discussed by the *Ariad* court, in evaluating a claim for compliance with the written description requirement of 35 U.S.C. 112, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date" although, as further noted by the court "'possession as shown in the disclosure' is a more complete formulation." Thus, "the test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on ***that*** inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed" (emphasis added). However, the court also notes that "written description does not ***demand*** either examples or a reduction to practice" (emphasis added). Rather, "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology". In particular, the court identifies "a number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." As such, "the number of species that must be disclosed to describe a genus claim… necessarily changes with each invention, and it changes with the progress in a field."

8. In the instant case, the claims are drawn to a method of screening for a substance which improves a vascular cell disorder which occurs due to the function of Rac protein (i.e., due to the transfer of Rac protein into the nucleus of the cell) by adding a substance to a cell and monitoring the transfer of Rac protein into nucleus of the cell.

9. **The Extent and Content of the Prior Art/Existing Knowledge in the Particular Field**: The instantly claimed invention pertains to methods of screening for a substance which improves a vascular cell disorder which occurs due to the function of Rac protein - or screening for a substance that inhibits the function of Rac protein - (i.e., due to the transfer of Rac protein into the nucleus of the cell) by adding a substance to a cell and monitoring the transfer of Rac protein into nucleus of the cell. At the time the instant application was filed, it would have been known by those of ordinary skill in the art that the Rho GTPase, **Rac** protein, plays a key role in a variety of vascular cell disorders (i.e., vascular diseases) via regulation of NADPH oxidase and the promotion of oxidant production which, given the cellular location of NADPH oxidase, takes place largely at the cell membrane (*Gregg et al*, Am J Physiol Cell Physiol 285:C723-C734, 2003). Furthermore, it was known that **Rac** is targeted to the plasma membrane via post-translational addition of a carboxy-terminal geranylgeranyl moiety derived from the mevalonate pathway (*Gregg et al*, Am J Physiol Cell Physiol 285:C723-C734, 2003). However, it was also known that **Rac** contains a C-terminal polybasic region (PBR) which acts as a nuclear localization signal (NLS), and that nuclear accumulation of **Rac** (alone or with associated proteins) can be promoted by conversion to the GTP-bound state (*Lanning et al*, J Biol Chem 278:12495-12506, 1/27/2003). Although it was believed that regulation of **Rac** may underlie some of the clinical benefits of statins (*Gregg et al*, Am J Physiol Cell Physiol 285:C723-C734,

2003), the translocation of **Rac** into the nucleus (and, thus, away from the cytosol and/or cell membrane where **Rac** can interact with NADPH oxidase) was not considered by the art as the mechanism by which statins regulate **Rac**.

10. **The Maturity of the Science/Technology**: At the time the invention was made, the science was extremely immature. Indeed, although it was known that **Rac** plays a role in vascular disease and that statins likely exert their clinical effects via regulation of **Rac**, Applicant appears to have been the first to observe that exposure of endothelial cells to the statin **pitavastatin** promotes translocation of **Rac** to the nucleus. Considering that the pathological actions of **Rac** take place largely at the cell membrane, it would have been reasonable (in view of Applicant's discovery) to hypothesize that statins may exert their beneficial effects by promoting the translocation of **Rac** to the nucleus and, thus, away from the cytosol and/or cell membrane where **Rac** can interact with NADPH oxidase. As such, it would have also been reasonable to further hypothesize that ***other substances*** which similarly promote the translocation of **Rac** to the nucleus (and, thus, away from the cytosol and/or cell membrane where **Rac** can interact with NADPH oxidase) would similarly exert beneficial effects. Significantly, however, both hypotheses remain untested. That is, Applicant does not provide any evidence what-so-ever that enhanced nuclear localization of **Rac** underlies statin activity or that ***other substances*** that promote nuclear localization of **Rac** are useful in the treatment of vascular disease. Nor is there anything to suggest that translocation of **Rac** to the nucleus ***inhibits the function*** of **Rac** as broadly recited by claims 21-24. That is, even though it may be hypothesized that substances which promote the translocation of **Rac** to the nucleus and, thus, away from the cytosol and/or

cell membrane where **Rac**, would inhibit the ability of **Rac** to interact with NADPH oxidase (one function of **Rac**) there is nothing to suggest other functions of **Rac** are inhibited.

11. **The Predictability of the Aspect at Issue**: As indicated above, considering that the pathological actions of **Rac** take place largely at the cell membrane, it would have been reasonable (in view of Applicant's discovery that **Rac** is translocated to the nucleus following statin treatment) to hypothesize that statins may exert their beneficial effects by promoting the translocation of **Rac** to the nucleus and, thus, away from the cytosol and/or cell membrane where **Rac** can interact with NADPH oxidase. As such, it would have also been reasonable to further hypothesize that ***other substances*** which similarly promote the translocation of **Rac** to the nucleus (and, thus, away from the cytosol and/or cell membrane where **Rac** can interact with NADPH oxidase) would similarly exert beneficial effects. However, many reasonable hypotheses turn out to be incorrect and, in the instant case, it is highly unpredictable whether enhanced nuclear localization of **Rac** does, in fact, underlie statin activity and/or whether ***other substances*** that promote nuclear localization of **Rac** would, in fact, be useful in the treatment of vascular disease. Indeed, it is equally plausible that **Rac** localization to the nucleus following statin exposure has no role what-so-ever in the beneficial activity of the statins. For example, as taught by *Stancu et al* (J Cell Mol Med 5:378-387, 2001), statins inhibit prenylation of GTP-ases. And it is now known that "prenylation masks the NLS of Rac1 such that inhibiting prenylation [relocalizes] the protein to the nucleus" (*Abidi,* Nuclear Localization of the Rac1 GTPase, Page 122, 2008). Accordingly, it is entirely plausible that statins act by blocking the production geranylgeranyl moieties via inhibition of HMG-CoA reductase (*Gregg et al*, Am J Physiol Cell Physiol 285:C723-C734, 2003), thereby reducing geranylgeranylation (i.e., prenylation) of **Rac1**

such that it is no longer capable of being localized to the plasma membrane to exert its pathological consequences (recall that localization of **Rac1** to the plasma membrane requires post-translational addition of a carboxy-terminal geranylgeranyl moiety) and, **as a consequence**, in this non-prenylated state, the NLS of **Rac1** is not masked and thus **Rac1** localizes to the nucleus instead. However, it is **not** the localization of **Rac1** to the nucleus which underlies or explains the effects of statins. Rather, it is the reduction of activated **Rac1** at the plasma membrane due to the inhibition of **Rac1** prenylation that underlies the mechanism of statins. The subsequent nuclear localization of non-prenylated **Rac1** is merely an unrelated, albeit inevitable, consequence. As such, it cannot be concluded that **other agents** which promote **Rac1** localization to the nucleus (including agents which promote at least as much transfer as pitavastatin promtes (as recited by new claim 25)) would be effective in improving a vascular cell disorder due to the function of **Rac**, as recited by the instant claims. Furthermore, it cannot be conluded that **Rac**, once translocated to the nucleus, is non-functional (as recited by claims 21-24).

12. In view of all of the foregoing, it is clear that the instant functional claims simply claim a desired result (i.e., screening for a substance that improves a vascular cell disorder which occurs due to the function of Rac (or inhibiting the function of Rac), wherein said substance is identified as such as substance if said substance promotes transfer of Rac protein into the nucleus), and does so without describing species that achieve that result. In particular, no vascular cell disorders wherein transfer of Rac protein into the nucleus underlies said disorder are provided such that identifying substances which promote the transfer of Rac protein (as recited by the claims) can reasonably be considered as evidence that the substance can improve a vascular cell

disorder. Accordingly, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. **Claims 13-16 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for screening for a substance which improves endothelial functions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims**.

14. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

15. **Nature of the invention and Breadth of the Claims**: The instant invention is drawn to a method of screening for a substance which improves a vascular cell disorder (or inhibits the function of Rac), which comprises labeling a Rac protein in a HUVEC, adding a test substance to a said HUVEC, and measuring (15 hours after addition of said test substance, as recited by instant claim 16) the transfer of Rac protein into the nucleus of said HUVEC (claim 13), more specifically wherein the Rac protein is in the form of a fusion protein which includes a fluorescent protein (claim 14) and/or wherein the transfer of labeled Rac protein into the nucleus is measured by observation with fluorescence (claim 15), even more specifically, wherein the

amount of Rac transferred is at least as much as the amount transferred by pitavastatin (claim 25).

16. As such, the nature of the invention is complex in that it provides for a method of identifying unknown substances which improve a vascular cell disorder or inhibit the function of Rac. As such, the claims are extremely broad in that **any** test substance can be added and screened for its ability to improve **any** vascular cell disorder or inhibit "the function" or Rac. Furthermore, the claims are broad in that the method involves measuring the transfer of Rac protein into the nucleus but, with the exception of claim 25, the method does not specify the **amount** of Rac protein transfer to the nucleus that must be measured to indicate that the test compound is capable of being used to improve said disorders. Thus, the breadth of the claims is extreme broad, which further exacerbates the complexity of the invention.

17. **Guidance of the specification/The existence of working examples**: The amount of direction provided by the Applicant is considered to be determined by the specification and the working examples. In the instant case, Applicant has provided data which allegedly indicate that Rac protein is transported into the nucleus of HUVECs (Page 14) following treatment with pitavastatin which, as taught by *Masamura et al* (Aterioscler Thromb Vasc Biol 23:512-517, 2003; cited in a previous Action), is an HMG CoA reductase inhibitor useful for the treatment of vascular conditions and disorders (Abstract). However, as discussed in the previous Action, and in detail above, Applicant's data do **not** demonstrate that the observed translocation of Rac into the nucleus is in any way responsible for pitavastatin's therapeutic effects. That is, there is nothing to suggest that the transfer of Rac into the nucleus is necessary for a substance (such as pitavastatin) to improve endothelial function. For example, as taught by *Stancu et al* (J Cell Mol

Med 5:378-387, 2001), statins inhibit prenylation of GTP-ases. And it is now known that "prenylation masks the NLS of Rac1 such that inhibiting prenylation [relocalizes] the protein to the nucleus" (*Abidi et al*, Nuclear Localization of the Rac1 GTPase, Page 122). Accordingly, it is entirely plausible that statins act by blocking the production geranylgeranyl moieties via inhibition of HMG-CoA reductase (*Gregg et al*, Am J Physiol Cell Physiol 285:C723-C734, 2003), thereby reducing geranylgeranylation (i.e., prenylation) of **Rac1** such that it is no longer capable of being localized to the plasma membrane to exert its pathological consequences (recall that localization of **Rac1** to the plasma membrane requires post-translational addition of a carboxy-terminal geranylgeranyl moiety) and, **as a consequence**, in this non-prenylated state, the NLS of **Rac1** is not masked and thus **Rac1** localizes to the nucleus instead. However, it is **not** the localization of **Rac1** to the nucleus which underlies or explains the effects of statins. Rather, it is the reduction of activated **Rac1** at the plasma membrane due to the inhibition of **Rac1** prenylation that underlies the mechanism of statins. The subsequent nuclear localization of non-prenylated **Rac1** is merely an unrelated, albeit inevitable, consequence.

18. Furthermore, there is nothing to suggest that translocation of **Rac** to the nucleus ***inhibits the function*** of **Rac** as broadly recited by claims 21-24. That is, even though it may be hypothesized that substances which promote the translocation of **Rac** to the nucleus and, thus, away from the cytosol and/or cell membrane where **Rac**, would inhibit the ability of **Rac** to interact with NADPH oxidase (one function of **Rac**) there is nothing to suggest other functions of **Rac** are inhibited.

19. Significantly, Applicant does not demonstrate that blocking the transfer of Rac into the nucleus also blocks the beneficial effects of pitavastatin or inhibits "the function" of Rac so as to

indicate that nuclear import of Rac is necessary for pitavastatin's therapeutic effects or Rac's "function". Accordingly, it is unclear whether adding any other test substance to a HUVEC and measuring the transfer of Rac protein into the nucleus would in any way indicate that the test substance is capable of improving a vascular cell disorder as recited by instant claims, or inhibiting "the function" of Rac as recited by the instant claims.

20. **State of the art/Predictability of the art**: The level of predictability in the art is considered to be relatively low.

21. **Amount of experimentation necessary**: Given the complex nature of the invention, which is exacerbated by the breadth of the claims, and given the lack of working examples and the high degree of unpredictability in the art, it would require undue experimentation for a person of ordinary skill in the art to use the invention as claimed. Since any compound that promotes any transfer of Rac protein into the nucleus would qualify as an agent capable of improving any vascular cell disorder according to the instant method (and further, considering there is no demonstrated connection between Rac nuclear transport and endothelial function improving ability), it would require undue experimentation to identify which of the test compounds are actually capable of being used to improve a vascular cell disorder.

Response to Applicant's Arguments

22. Applicant argues that, based on *Masamura et al*, "Rac is geranylated and thus activated when outside the nucleus" (Applicant Arguments, Page 6). Since pitavastatin promotes the "movement of Rac proteins to the nucleus", it thus "reduces the number of proteins to be geranylated and activated on the cell surface or in the cytosol" (Applicant Arguments, Pages 6-7). That is, as argued by Applicant, "[w]hen pitavastatin is added, Rac proteins are moved to the

inside of the nucleus before they are geanylgeranylated... [and] makes the unactivated Rac protein unavailable for activation. Thus, less activated Rac protein adheres to the cell membrane, causing an improvement of vascular function" (Applicant's Arguments, Page 7). Applicant's argument, however, brings to mind the idiom of "putting the cart before the horse". That is, there is nothing to suggest that it is the localization of Rac proteins to the nucleus which reduces their activity at the cell membrane (as asserted by Applicant). Rather, as discussed above, it is equally plausible (and, arguably, ***more*** plausible) that statins act by blocking the production geranylgeranyl moieties via inhibition of HMG-CoA reductase (*Gregg et al*, Am J Physiol Cell Physiol 285:C723-C734, 2003), thereby reducing geranylgeranylation (i.e., prenylation) of **Rac1** such that it is no longer capable of being localized to the plasma membrane to exert its pathological consequences (recall that localization of **Rac1** to the plasma membrane requires post-translational addition of a carboxy-terminal geranylgeranyl moiety) and, **as a consequence**, in this non-prenylated state, the NLS of **Rac1** is not masked and thus **Rac1** localizes to the nucleus instead. Thus, even if **other agents** which promote **Rac1** localization to the nucleus (including agents which promote at least as much transfer as pitavastatin promotes (as recited by new claim 25)), there is nothing to suggest that these agents would be effective in improving a vascular cell disorder due to the function of **Rac**.

23. For all the foregoing reasons, Applicant's arguments are not found persuasive.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. **Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Krall et al* (Infection and Immunity 70:360-367, 2002) and *Essler et al* (Cellular Signaling 14:607-613, 2002)**.

27. Claims 17-20 are drawn to a method of screening for a substance that promotes nuclear transfer of a protein, said method comprising labeling a Rac protein in a HUVEC, adding a test substance to a said HUVEC, and measuring (15 hours after addition of said test substance, as recited by instant claim 20) the transfer of Rac protein into the nucleus of said HUVEC (claim 17), more specifically wherein the Rac protein is in the form of a fusion protein which includes a fluorescent protein (claim 18) and/or wherein the transfer of labeled Rac protein into the nucleus is measured by observation with fluorescence (claim 17).

28. *Krall et al* teach methods for monitoring the nuclear uptake of **Rac protein** comprising adding a test substance to a cell which contains labeled **Rac protein** (more specifically wherein the **Rac protein** is in the form of a fusion protein which includes a fluorescent protein (claim 18)) and measuring the transfer of Rac protein into the nucleus of said cell (claim 17) (more

specifically, wherein the transfer of labeled Rac protein into the nucleus is measured by observation with fluorescence (claim 17)).

29. As such, *Krall et al* differs from the instantly claimed invention in that the methods take place in cells which are not HUVECs as instantly claimed.

30. Yet, as taught by *Essler et al*, HUVEC contain Rac proteins.

31. Accordingly, it would have been *prima facie* obvious to substitute one known cell comprising **Rac proteins** (i.e., CHO cells as taught by *Krall et al*) with another known cell comprising Rac proteins (i.e., HUVECs as taught by *Essler et al*) to investigate Rac protein localization with a reasonable expectation of success. The skilled artisan, investigating whether certain compounds promote Rac localization to the nucleus in CHO cells (as taught by *Krall et al*) would have reasonably predicted that substituting HUVEC cells in place of CHO cells would provide the same results, based on *Essler et al*.

32. As such, claims 17-19 are rejected as *prima facie* obvious.

33. As to claim 20, as argued by Applicant, "the period of time over which the HUVEC should be monitored for Rac transfer depends on the culture condition of the HUVEC. This can be suitably determined by one having ordinary skill in the art" and that "the approximate stimulus-response time in HUVEC is well known among those skilled in the art. As such, the time period for the claimed embodiments could have readily been determined in accordance with the common knowledge in the art, without requiring undue experimentation" (Applicant Argument, Page 12). In view of the foregoing, it is asserted that the skilled artisan would have found it *prima facie* obvious to measure the transfer of labeled Rac protein into the nucleus by observation with fluorescence 15 hours after addition of the test substance based on the culture

condition of the HUVEC, the well-known stimulus-response time in HUVEC and common knowledge in the art. Accordingly, instant claim 20 is also rejected as *prima facie* obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628